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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
11/10/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/531,726	KLIPPEL-GIESE ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2008*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65-68 and 73-85* is/are pending in the application.
4a) Of the above claim(s) *66,67, 76 and 77* is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *65,68,73-75 and 79-85* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☒ All b)☐ Some * c)☐ None of:
1.☒ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/5/09*.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5)☐ Notice of Informal Patent Application
6)☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/5/09 has been entered.

Claims 86 and 87 were added. Claims 65-68 and 73-87 are pending.

Claims 66, 67, 76, 77 stand withdrawn as being drawn to an non-elected invention.

Claims 65, 68, 73-75 and 79-87 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 65, 68, 73-75 and 79-87 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 65 and 68 are drawn to methods of controlling the metastatic or migrational activity of tumor or cancer cells by contacting tumor or cancer cells with a composition comprising an siRNA that inhibits the activity of PRF1. PRF1 was also known in the prior art as REDD1, RPT801, and HOG18. Claim 86 further limits the invention by requiring administration to the prostate of an individual with prostate cancer.

Claims 73-75 and 79-85 are drawn to methods of inhibiting the growth of tumor cells of a precancerous growth having dysregulation of PI-3-kinase signaling and hyperactivation of the HIF-1alpha signaling pathway, and/or hyperactivation of AKT signaling, by administering to a subject a composition comprising an siRNA that inhibits the activity of PRF1. Claim 88 further limits the invention by requiring administration to the prostate of an individual with prostate cancer.

None of the claims limits the mode of administration.

The instant invention is based on the observations that transcription of PRF1 is regulated by one or more of the diverse PI3K signaling pathways, and that inhibition of PRF1 expression in PC-3 prostate cancer cells resulted in a decrease in cell growth. The specification presents evidence that this transcriptional activation occurs downstream of HIF1 alpha and Akt in two of the myriad PI3K pathways, and that PRF1 is located downstream of mammalian target of rapamycin (mTOR) in the PI3K network, but provides no further guidance as to the biochemical function of PRF1.

PI3Ks constitute a family of enzymes that respond to stimuli from various receptors to produce 3' phosphoinositide lipids that act as second messengers by binding to diverse cellular target proteins to influence a variety of cellular activities including proliferation, differentiation, chemotaxis, survival/apoptosis, intracellular trafficking, and glucose homeostasis. See Katso et al (Annu. Rev. Dev. Biol. 17: 615-675, 2001). Katso states that the factors that determine which cellular function is mediated by a PI3K are complex and may be partly attributed to the diversity that exists at each level of the PI3K signaling cascade, such as the type of stimulus, duration of stimulus, the isoform of PI3K, the nature and intracellular location of the second messenger lipids, and the developmental state of the cell or organism. Further, the spatial and temporal aspects of PI3K signaling, functional redundancy, and crosstalk with other signaling networks are also thought to influence the integration of a given stimulus. See abstract, and page 655, first paragraph of Perspective.

Fig. 1 at page 624 of Katso gives some idea of the enormous complexity of PI3K signaling. Stimuli, both positive and negative, include Fak, shear stress, Cbl, Ruk, tyrosine kinase receptors, cytokines, integrins, cadherin, and G protein coupled receptors. Second messenger PIP_3 interacts with diverse entities including BTK/Tec kinases, PDKI, PKD, and GEFs. These interactions give rise to overlapping as well as independent cascades of activity that result in a variety of outcomes including proliferation, differentiation, chemotaxis, survival/apoptosis, trafficking, and glucose homeostasis. Note that many factors known to be involved in PI3K signaling are not even represented in the Fig (such as Akt and HIF1-alpha). Thus, those of skill in the art

at the time of the invention recognized that the effects of PI3K signaling in a given cell were influenced by a complex multitude of factors that constitute nodes in a network of signaling cascades extending from PI3K that controls the activity of a variety of proteins and the transcription of various sets of genes. Possible outcomes of PI3K stimulation include opposing effects such as cellular proliferation to apoptosis.

The specification as filed teaches that PRF1 seems to be regulated by both the HIF alpha and AKT branches of the PI3K network and acts downstream of mammalian target of rapamycin (mTOR). The specification indicates that a decrease in the expression or activity of PRF1 is suitable to put a cellular system into a condition corresponding to hypoxic conditions, which may lead to apoptosis, so inhibition of PRF1 can stimulate apoptosis for therapeutic purposes in tumor treatment. See pages 12 and 18 (paragraphs 56 and 70 of the published application). However, Fig. 1 of Katso discloses at least two other pathways by which PI3K can inhibit apoptosis (i.e. through stimulation of IKK or inhibition of BAD), and the relationship of these pathways to PRF1 is not known.

It is clear that not all aspects of the PI3K network are functional in all cells, and it follows that an agent that acts on a branch of the network that does not function in a given cell would not be expected to have any predictable effect on that cell. It is noted that the pathway steps that lead directly to regulation of PRF1 transcription or activity were not completely understood at the time of filing, and neither were the pathway steps directly downstream of PRF1 expression and activity, and its possible interactions with other signaling pathways. Accordingly, the effects of manipulating PRF1 expression

were unpredictable at the time of filing, and had to be determined on a case by case basis for different tumors.

Absent information regarding which pathways are operating in a given cell at a given time, and the effects of PRF1 on those pathways, it would be completely unpredictable as to whether inhibition of PRF1 would stimulate apoptosis or not, because the effects of PRF1 inhibition on the other relevant apoptosis-affecting pathways are unknown. The specification provides no guidance in this regard, except to indicate that because PRF1 is at a downstream point in the network, it should be close to the point of action and unintended consequences should be limited. However, the relationship of PRF1 to other branches of the PI3K network involved in apoptosis control was unknown at the time of filing, so the effects of PRF1 inhibition on cell survival were not predictable. Note also that status of PI3K independent signaling pathways that affect apoptosis and cell survival would need to be taken into account in order to accurately predict the effects of such inhibiting PRF1 (see Katso at page 656, last paragraph).

At the time the invention was filed, the in vivo function of PRF1 was not well characterized. Shoshani et al (Mol. Cell. Biol. 22(7): 2283-2293, 2002, of record) identified RTP801 (PRF1) as a novel gene encoding a protein without any defined structural domains that was upregulated sharply in glioma cells in response to hypoxia. They showed that PRF1 could either promote, or protect cells from, apoptosis and that these functions of PRF1 were dependent on the context of the cell in which it was expressed. PRF1 protected two secondary tumor cell lines from apoptosis under

conditions of rapid cell division, while promoting apoptosis in both of those lines, as well as in primary non-cancerous lung parenchymal cells in vivo, under non-rapidly dividing conditions. However, Shoshani did not make a generalized conclusion that PRF1 caused apoptosis in rapidly dividing cells, but instead concluded that the involvement of PRF in pathogenic disease was complex and noted the importance of further study regarding its roles in dividing and non-dividing cells. See abstract and page 2292, last three paragraphs. Thus, prior to the time of the instant invention, it was recognized that PRF1 could either promote or inhibit cellular proliferation, depending on the context in which it was expressed. The actual biochemical function of PRF1 in PI3K signaling, i.e. enzyme, binding factor, etc., and its relationship to other PI3K pathways affecting apoptosis was not known at the time of the invention. Absent more information as to the actual biochemical function of PFR1, and the further study indicated as important by Shoshani, it is considered unpredictable as to what would be the effects of PRF1 expression inhibition in cells generally in view of the complexity of the PI3K signaling network.

The post filing art provides further evidence of unpredictability regarding the role of PRF1 in proliferative disease. DeYoung et al (Genes Dev. 22: 239-251, 2008) showed that PRF1 (identified as REDD1) can contribute to tumor suppression in secondary tumor cells. “In vitro, loss of REDD1 signaling promotes proliferation and anchorage-independent growth under hypoxia through mTORC1 dysregulation. In vivo, REDD1 loss elicits tumorigenesis in a mouse model, and down-regulation of REDD1 is observed in a subset of human cancers.” See abstract and section entitled

"*Endogenous REDD1 functions to suppress tumorigenesis in vivo*" at page 246. Note that DeYoung states that a similar frequency of REDD1 downregulation was observed in a comparison of normal prostate tissue to invasive primary prostate carcinomas (citing LaPointe (Proc. Nat. Acad. Sci. 101(3): 811-816, 2004)). DeYoung concludes that "[t]aken together, these findings support the view that the endogenous REDD1 pathway... functions as a tumor suppressor mechanism in vivo" (page 246, right column, end of first full paragraph). See also Fig. 8 on page 248, which presents a model for the activity of REDD1 as a tumor suppressor. Clearly, if PRF1 (REDD1) acts as a tumor suppressor in some cells, then one of skill could not have predictably used inhibitors of its activity to inhibit the growth of tumors or precancerous cells without further knowledge of the function of PRF1 in those particular cells.

Other prior art references provide a correlation between PRF1 expression and cancer cells as follows.

Riggins et al (US 20030207840, effective filing date 7/26/01 (US 60/307600)) identified several genes that were induced in a variety of tumor cells in response to hypoxia. These genes included HOG18 (SEQ ID NO: 5) which encodes a polypeptide identical to PRF1. Riggins suggests that conditions related to angiogenesis, such as tumor growth, could be treated by disrupting expression of HOG18. See abstract, paragraphs 9, 13, 22, 32, 33, 37, and 47; SEQ ID NOS: 5 and 6; and claims 12-14. Riggins does not provide a working example of tumor growth inhibition.

Monahan et al (US 20050037010, effective filing date 8/20/02 (US 60/404770)) taught that PRF1 (termed M22A or RTP801 by Monahan) was overexpressed in

cervical cancer cells compared to normal cervical cells, and suggested that tumors could be treated with antisense that inhibits PRF1 expression. See paragraphs 62, 113, 159, 365, 368, and 371; SEQ ID NOS: 39 and 40; Table 1 at page 37; Table 5 at last line of page 38; Table 8 on page 40; and claim 40. Monahan does not provide a working example of tumor growth inhibition.

Faris et al (US 6673545) disclosed that a nucleic acid encoding instant PRF1 was overexpressed in metastatic prostate adenocarcinoma cells, relative to non-metastatic prostate adenocarcinoma cells. See Table 1 and column 4, lines 12-23. The nucleic acid is disclosed as SEQ ID NO: 45, also denoted in Table 4 as clone ID 3120209.

In view of the facts that, at the time of the invention, the control of the cell cycle by PI3K-mediated events was considered to be extremely complicated, the role of PRF1 in this process was incompletely understood, the biochemical function of PRF1 was unknown, and PRF1 was observed to elicit opposite effects on cell survival in different contexts, it is considered to be highly unpredictable as to what the effects of PRF1 expression inhibition would have been in vivo in tumor or precancerous cells generally. This unpredictability is borne out in the post filing art (DeYoung, LaPointe, above) which suggests that PRF1 is a tumor suppressor in breast tumor cells, and is underexpressed in primary prostate carcinoma cells. Accordingly, one of skill in the art at the time of the invention could not have known generally in which primary tumor or precancerous cells in vivo the invention would function as claimed. Because the specification and prior art do not provide information as to how to predict which tumor or precancerous cells will

be inhibited by PRF1 siRNA, one of skill in the art would have had to perform undue experimentation in order to practice the invention as claimed.

In addition to the unpredictability associated with the function of PRF1 in vivo, the complexity of the PI3K network, and status of the network in a given cell, those of skill in the art at the time of the invention, and after the invention, recognized significant obstacles related to the predictability of inhibiting expression of a target gene *in vivo* by RNA interference (RNAi), particularly in regards to the *in vivo* targeting and delivery of specific nucleic acids that mediate RNAi to the appropriate cell/organ, at a bio-effective concentration and for a period of time such that said molecule is effective in inhibiting expression of a target gene. Indeed, nucleic acid based therapies at the time of filing were highly unpredictable and while it is recognized that introduction of dsRNA targeted to a specific gene may result in expression inhibition, the successful delivery of dsRNA to a target cell *in vivo*, such that the requisite biological effect was provided to the target cells/tissues/organs, must be determined empirically.

The state of the art at the time of filing shows that RNA interference was recognized as not enabled for therapeutic purposes. (See for example, Caplen 2003, Expert Opin. Biol. Ther. 2003, Vol. 3, pp. 575-586; Coburn et al. 2003, Journal of Antimicrobial Chemotherapy. Vol. 51, pp. 753-756; Agami et al. 2002 Current Opinion in Chemical Biology. Vol. 6, pp. 829-834) for reviews on the progression of RNA interference in mammalian cells and the state of the art of RNA interference for therapeutic purposes).

Opalinska et al. (Nature Reviews Drug Discovery, 2002, Vol. 1, pp. 503-514) stated, “[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA”, and in column 2 of the same page, “[a]nother problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded.”

Caplen (2003) taught out that, "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system...". (pg. 581).

Coburn et al. (2003) taught that the major impediment to using RNA interference as a therapeutic is that suppression of gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example p 754, first column, last paragraph).

Check (Nature, 2003, Vol., 425, pp. 10-12) reported "…scientists must figure out how to make RNAi therapies work. They are facing some formidable technical barriers, chief among which is the problem of getting siRNAs into the right cells. This is not a trivial issue, because RNA is rapidly broken down in the bloodstream and our cells don't readily absorb it through their membranes. And even when RNA gets into its target cell, scavenger proteins quickly chew it up." (see page 11, middle column, second full paragraph). Check describes that delivery methods are of concern to many researchers. In column 2 of page 11: " …'The major hurdle right now is delivery, delivery, delivery' says Sharp" and in column 3 of the same page, "Khvorova believes that the medical benefits of RNAi will be huge if the delivery issues can be resolved. 'But we've looked at a lot of the delivery methods that have been used for antisense, and so far I haven't been impressed,' she says."

After the time of the invention, Zhang et al (Current Pharmaceutical Biotechnology 2004, Vol. 5, pp.1-7) reviewed the state of the art with regard to RNAi, and stated "[u]se of siRNA in mammalian cells could be just as far-reaching, with the applications extending to functional genomics and therapeutics. But various technical issues must be addressed, especially for large-scale applications. For instance, dsRNA can be delivered to *C. elegans* by feeding or soaking, but effective delivery of siRNAs to mammalian cells will not be so simple."

Thus it is abundantly clear that it was not routine prior to and after the time of the invention for those of skill in the art to perform therapy by delivery of siRNA to target

cells in vivo, particularly by methods other than those that allow delivery directly to the target cells.

In particular regards to Applicant's *ex vivo* example, often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism). For example, Agrawal et al (Agrawal et al. (Mol. Med. Today 6:72-81, 2000) stated "[t]he cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*in vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Agrawal discussed these factors in relation to antisense, but they would also apply to dsRNA. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies").

In regards to the amount of direction provided by Applicant as to how one of skill in the art would practice the full scope of the claimed invention, the specification as filed does not disclose any delivery formulations or techniques that were not available in the prior art, and so does not adequately address the state of the art at the time of the invention with regard to siRNA delivery to target cells in vivo.

After considering the totality of evidence, in particular the unpredictability associated with the function of PRF1 in vivo, the complexity of the PI3K network, the

status of the network in a given cell, and the difficulty associated with systemic delivery of siRNAs in vivo, as well as the states of these arts, and the amounts of exemplification and guidance in the specification, the Office finds that one of skill in the art could not practice the invention was claimed without undue experimentation.

Response to Arguments

Applicant's arguments filed 10/5/09 have been fully considered but they are not persuasive.

Applicants argues that those of skill in the art at the time of the invention would not have had a basis to doubt the teachings of the as-filed specification which shows that inhibition of PRF1 inhibited the metastasis of prostate carcinoma cells and inhibited growth of tumors arising from prostate cancer cells, relying for support on specification examples 5, 9, and 10. IN this regard, Applicants arguments are unpersuasive because they rely on results obtained with a single prostate tumor cell line, PC-3. As discussed in the rejection, the filed of the invention is considered to be unpredictable because the elements of the PI3K network that are active in a given cell depend on the type of cell in question as well as the state of the cell at any given time. Thus the results obtained in PC-3 cells cannot be extrapolated reasonably to other tumor cells because the role of PRF1 in these cells was not known. Evidence for this comes from Shoshani who showed that PRF1 could either promote, or protect cells from apoptosis, indicated that these functions of PRF1 were dependent on the context of the cell in which it was expressed, and concluded that the involvement of PRF in pathogenic disease was

complex and noted the importance of further study regarding its roles in dividing and non-dividing cells. See abstract and page 2292, last three paragraphs. Thus, prior to the time of the instant invention, it was recognized that PRF1 could either promote or inhibit cellular proliferation, depending on the cellular context in which it was expressed. The actual biochemical function of PRF1 in PI3K signaling, i.e. enzyme, binding factor, *etc*., and its relationship to other PI3K pathways affecting apoptosis was not known at the time of the invention. Absent more information as to the actual biochemical function of PFR1, and the further study indicated as important by Shoshani, it was unpredictable as to what would be the effects of PRF1 expression inhibition in cells other than PC-3 cells in view of the complexity of the PI3K signaling network and the varying states of the network in different cell types.

Further evidence of the unpredictability of the art comes from DeYoung (2008) who showed that PRF1 acted as a tumor suppressor in transformed mouse embryo fibroblasts with hyperactivated AKT, and concluded that "[l]oss of REDD1-dependent signaling therefore promotes in vivo tumorigenesis in murine cells." DeYoung also stated that REDD1 was downregulated in 8 of 27 breast carcinoma specimens compared to tissue matched controls, and that a similar frequency of REDD1 downregulation was observed in prostate carcinomas. See page 246, section entitled "Endogenous REDD1 functions to suppress tumorigenesis in vivo". This is objective post-filing evidence of the unpredictable nature of the function of PRF1 in cancer that substantiates the unpredictability noted by Shoshani in the prior art. Clearly, if PRF1 (REDD1) acts as a tumor suppressor in some cells, then one of skill could not have

predictably used inhibitors of its activity to inhibit the growth of tumors or precancerous cells without further knowledge of the function of PRF1 in those particular cells.

Regarding the reference by DeYoung to LaPointe (Proc. Nat. Acad. Sci. 101(3): 811-816, 2004) regarding REDD1 downregulation in a comparison of normal prostate tissue to invasive primary prostate carcinomas, Applicants state that they have reviewed the La Pointe publication and have been unable to find any basis for this teaching, or any mention of PRF1 or its aliases. The Examiner is similarly unable to find any specific reference to PRF1 in the article by LaPointe, but notes that Fig. 1 does not label all of the genes assayed in the study. The legend to Fig. 1 indicated that the complete data set was available at http://microarray-pubs.stanford.edu/prostateCA. It is possible that DeYoung et al arrived at their conclusion after analysis of those data. In any case, the data of LaPointe are not necessary to establish the unpredictability of the instant subject matter. This unpredictability is established by Shoshani, prior to the time of the invention, and substantiated by DeYoung after it, even without reference to La Pointe as discussed above.

Applicant also notes that several references supplied by the Examiner identified overexpression of PRF1 and associated this overexpression with tumorigenesis and/or metastasis. However, none of these references provided a working example of PRF1 inhibition. Each of them only speculated that inhibition of PRF1 might have anti-tumor effects, and the speculation was not based on studies that excluded other candidate genes that could have caused the effect. In contrast, both Shoshani and DeYoung provided objective evidence that PRF1 could inhibit proliferation, and that inhibition of

PRF1 could lead to cellular proliferation. This evidence must receive more weight in the enablement analysis than does speculation based on association studies.

Finally, Applicant argues that the specification as filed enables systemic delivery of oligonucleotides, particularly in view of working examples in the prior art. The Office acknowledges that there are examples of the successful systemic delivery of oligonucleotides in the prior art. However, the Office also holds that state of the art at the time the invention was filed indicated substantial difficulty in the field of delivering oligonucleotide drugs in vivo. The state of the art of oligonucleotide delivery is only one facet of the entire enablement analysis. Even if in vivo oligonucleotide delivery was routine, the claims would not be considered to be enabled in view of the unpredictability in the art regarding the role of PRF1 in tumor growth and metastasis as established above and in the rejection. For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Tracy Vivlemore, can be reached at (571) 272-0763. The official central fax

number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer/
Primary Examiner, Art Unit 1635